CLOSER LOOK

MEMORANDUM

JAMA publishes two CGM in MDI studies: Dexcom's DIaMonD trial and the GOLD study in Sweden; hopefully reimbursement victories to influence skeptical payers - January 25, 2017

Executive Highlights

- On Tuesday, JAMA published two positive CGM in MDI studies: Dexcom's DIaMonD study (first presented at ADA 2016; Beck et al.) and the Swedish GOLD study (Lind et al.).
- Both randomized trials used Dexcom's G4 in type 1 adults on MDI, and both found similar A1c advantages with CGM over SMBG (0.4%-0.6%). Secondary endpoints were also consistent, including significantly less time in hypo/hyperglycemia and more time-in-range.
- Notably, DIaMonD now reports a "1.0%" A1c reduction in the CGM group, a huge rounding win for Dexcom as the ADA presentation implied (to us) a 0.9% reduction with CGM (8.6% -> 7.7%). That's a small but very meaningful difference for perceptions of CGM's clinical effectiveness. We'll see more DIaMonD data at ATTD - from the type 2 phase and the crossover to pump therapy.
- Dr. Mayer Davidson wrote a very underwhelming editorial, focusing mostly on the "caveats" to the data - we think this commentary missed the mark for reasons discussed below.
- We see these important RCTs in a major journal like JAMA as a key evidence victory for the field, showing CGM works very well in MDIs. Hopefully they are a positive for reimbursement, including with private payers (reducing hassle, improving coverage to non-pumpers) and as Dexcom seeks Medicare coverage.

On Tuesday, JAMA published two very important and positive CGM in MDI studies: Dexcom's DIaMonD study (first presented at ADA 2016; Beck et al.; n=158) and the investigator-initiated Swedish GOLD study (Lind et al.; n= 161). Both randomized trials tested use of CGM over ~6 months vs. SMBG, showing similar outcomes with Dexcom's G4 in almost identical study populations of adult MDI users (mean age of 48 and 44 years), including:

- **Lower A1c levels (by ~0.4%-0.6%).** The DIaMonD publication reported a 1.0% reduction in A1c at 26 weeks with CGM vs. 0.4% for the parallel SMBG group (-0.6% difference, p<0.001). GOLD was a crossover design where participants used CGM and SMBG for 26 weeks each; the CGM period had a 0.4% A1c advantage (p<0.001). Both trials had a baseline A1c of 8.6%.
- **Less time in hypoglycemia <70 mg/dl**: In DIaMonD, CGM users spent a median of 43 minutes per day in hypoglycemia (a 34% improvement from baseline) vs. 80 minutes per day in the control group (11% MORE hypoglycemia) [p=0.002]. In GOLD, hypoglycemia was nearly halved with CGM use: 2.79% with CGM (40 minutes per day) vs. 4.79% (69 minutes per day) during SMBG [p <0.05].
- **More time-in-range (70-180 mg/dl):** In DIaMonD, CGM users spent an impressive 76 more minutes more per day in range (a 12% improvement from baseline), while SMBG users had zero change (p=0.005). In GOLD, CGM users spent 39 minute more per day in range vs. SMBG users (p<0.05).
- **Less time in hyperglycemia, among other outcomes shown in the tables below.**

We see these important RCTs in a major journal like JAMA as a key evidence victory for the field and hopefully a positive for reimbursement, including with private payers (reducing hassle, improving coverage to non-pumpers) and as Dexcom seeks Medicare coverage (since DIaMonD extended up to 73 year-olds). Though US CGM reimbursement among private payers is typically characterized as "great," we continue to

hear (and personally experience) administrative hassles to accessing CGM - prior authorization, insurance verifications, etc. (Dr. Korey Hood and colleagues reported similar cost concerns in their recent paper on barriers to pumps/CGM in the T1D Exchange, which mostly surveyed current users.)

A major goal of these studies was to build an evidence base for CGM in MDIs, which was sorely lacking. We wonder if these data could drive further prescribing of CGM among endocrinologists trained to think of pump first-CGM second. Dexcom has been emphasizing the "CGM first" message for years, and these data certainly support the value of this technology in MDI.

We'll see more DIaMonD data at ATTD - from the type 2 study population and the group that crossed over to add pump therapy (what does a pump add on top of CGM?).

Glucose monitoring skeptic Dr. Mayer Davidson wrote a an underwhelming accompanying editorial, focusing mostly on the "caveats" to the data: (i) CGM is still too expensive and may not be covered; (ii) the relative 0.4%-0.6% A1c improvements with CGM vs. SMBG are "modest"; (iii) longer studies are needed; (iv) CGM is still invasive and requires SMBG; (v) the investigators were experienced in using CGM in both trials; and (vi) the results are not generalizable to type 2s. We think this commentary missed the mark on several key points: (i) studies like this are needed to improve cost/coverage, and future technologies will be less expensive; (ii) A1c is a poor endpoint for devices like CGM that reduce lows and highs (benefit underestimated - indeed, mean glucose barely changed in either study); (iii) factory calibration is already here (FreeStyle Libre, though not a traditional CGM) and coming with a next-gen version of Dexcom's G6; (iv) these six-month studies are very long in the world of diabetes devices, and any longer would suffer from innovation lag using old sensor technology; (v) sensors are becoming less invasive, certainly with FreeStyle Libre and Dexcom/Verily; and (vi) type 2s may benefit even more from CGM than type 1s, since the real-time feedback from meals/exercise is 100x what they are getting right now from infrequent BGM.

Read more details below, including our key questions and study results.

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- **Those looking closely will see that the DIaMonD publication reported a "1.0%" reduction in A1c in the CGM group, a nice mark to hit and higher than the 0.9% improvement we inferred at ADA** (the slide at the time showed an 8.6% at baseline to 7.7% by the trial end in the CGM group). Lead author Dr. Roy Beck and Dexcom's Dr. David Price confirmed with us that this is due to rounding, and the 1.0% value in the publication is accurate. Certainly, what matters to payers is what's in the publication, and this small difference is a very meaningful win for Dexcom - e.g., "CGM can reduce A1c by 1.0%."
    - **The CGM-based outcomes are also slightly different for DIaMonD between ADA and the *JAMA* paper;** the ADA presentation compared baseline-week 24, while the paper compares baseline-weeks 12/24 pooled.
- **Dexcom's press release on the DIaMonD publication yesterday also emphasized the positive results came regardless of age or education** (something we also heard at ADA), a positive sign as it closes in on Medicare coverage (benefit category granted earlier this month) - 60+ year-olds benefitted as much as younger users.

    - **"Additionally, the study dispels the perception that CGM is too complicated to use**, as patients demonstrated significant A1c reductions regardless of education level, math ability, or age. A high level of adherence was also achieved with 93% of patients still using the Dexcom CGM System ≥6 days/week at the end of the study." - Dexcom's press release

- **Both GOLD and DIaMonD reported a non-significant trend towards fewer severe hypoglycemia events with CGM.** In GOLD, there were five events of severe hypoglycemia during conventional treatment (0.19 per 1,000 patient-years) vs. one event with CGM (0.04 per 1,000 patient-years). In DIaMonD, CGM trended towards less severe hypoglycemia: a 2% rate (two out of 105 patients) vs. a 4% rate in usual care (two out of 53 patients). We assume these would reach statistical significance in a larger study, or a study focused on hypoglycemia unaware patients (e.g., like the *Lancet Diabetes & Endocrinology* publication that came out at EASD 2016).

Close Concerns Questions

- Will HCPs see this data and be more willing to prescribe CGM in MDIs?
- Could these results improve CGM reimbursement? With what payers/health systems will they have the most impact?
- How will payers' view this data relative to the current evidence base?
- Are these results a positive for Dexcom alone, or also for Abbott and Medtronic and other upcoming CGMs?
- Could the DIaMonD data accelerate Medicare coverage for Dexcom's G5, following the positive benefit category ruling earlier this month?
- What will the type 2 and pump crossover data from DIaMonD show at ATTD? Will CGM have similar outcomes in type 2 as type 1?
- How good is CGM reimbursement right now in Sweden, and what does GOLD add in terms of expanding access?

DIaMonD Key Results

Read the JAMA publication here.

A1C

Table 2. Primary Outcome and Hemoglobin A_{1c} Outcomes at 12 and 24 Weeks[a]

	12 Weeks		24 Weeks			
	CGM Group (n = 103)	Control Group (n = 52)	CGM Group (n = 105)[b]	Control Group (n = 53)	Between-Group Difference[c,d]	*P* Value[c,d]
Primary outcome, mean (SD), %					Mean adjusted difference, % (95% CI)	
HbA_{1c}	7.6 (0.7)	8.1 (0.7)	7.7 (0.8)	8.2 (0.8)		
Change in HbA_{1c} from baseline	−1.1 (0.7)	−0.5 (0.7)	−1.0 (0.8)	−0.4 (0.7)	−0.6 (−0.8 to −0.3)	<.001
Prespecified secondary outcome, No. (%)					Mean adjusted difference, % (99% CI)	
HbA_{1c} <7.0%	14 (14)	2 (4)	18 (18)	2 (4)	15 (0 to 30)	.01
Prespecified exploratory outcomes, No. (%)						
HbA_{1c} <7.5%	49 (48)	6 (12)	39 (38)	6 (11)	31 (12 to 51)	<.001
Relative reduction in HbA_{1c} ≥10%	62 (60)	12 (23)	58 (57)	10 (19)	37 (16 to 58)	<.001
Post hoc outcomes, No. (%)						
Reduction in HbA_{1c} ≥1%	55 (53)	12 (23)	53 (52)	10 (19)	33 (11 to 54)	<.001
Reduction in HbA_{1c} ≥1% or HbA_{1c} <7.0%	57 (55)	12 (23)	53 (52)	11 (21)	31 (9 to 52)	<.001

Abbreviations: CGM, continuous glucose monitoring; HbA_{1c}, hemoglobin A_{1c}.

SI Conversion: to convert HbA_{1c} to the SI units of mmol/mol, multiply the HbA_{1c} percentage value × 10.93 and subtract 23.5 from the product.

[a] Mean baseline HbA_{1c} level was 8.6% in each group. For all analyses, missing HbA_{1c} values in which the central laboratory value was missing but the local laboratory value was known were imputed with a regression line based on the site's local HbA_{1c} measurements (CGM/control: 1/0 at 12 weeks; 1/0 at 24 weeks).

[b] For the 24-week primary outcome only, the Rubin method was used to impute missing HbA_{1c} values when both the central and local laboratory values were missing (3 in the CGM group and 0 in the control group). For the secondary, exploratory, and post hoc analyses, n = 102.

[c] For the primary analysis, treatment group comparisons were made with analysis of covariance models, adjusted for baseline HbA_{1c} level and clinical site as a random effect. Model residuals were verified to have an approximate normal distribution.

[d] For the secondary, exploratory, and post hoc outcomes, treatment group comparisons were made with propensity scores, adjusted for baseline HbA_{1c} level and clinical site. $P < .01$ was considered significant to account for multiple comparisons (with 99% CIs accordingly provided).

CGM METRICS

Table 3. Continuous Glucose Monitoring Metrics

	Baseline		12 and 24 Weeks Pooled[a]			
	CGM Group (n = 105)	Control Group (n = 53)	CGM Group (n = 103)	Control Group (n = 53)	Mean Adjusted Difference (99% CI)[b]	*P* Value[b]
Hours of data, mean (SD)	322 (50)	325 (51)	301 (41)	301 (54)		
Prespecified secondary outcomes						
Glucose variability: coefficient of variation, mean (SD), %	42 (7)	42 (7)	38 (6)	42 (7)	−4 (−6 to −2)	<.001
Minutes per day in range 70-180 mg/dL, mean (SD)	660 (179)	650 (170)	736 (206)	650 (194)	77 (6 to 147)	.005
Hypoglycemia, median (IQR)						
Minutes per day <70 mg/dL	65 (33 to 103)	72 (35 to 136)	43 (27 to 69)	80 (36 to 111)		.002
Minutes per day <60 mg/dL	32 (15 to 61)	39 (15 to 78)	20 (9 to 30)	40 (16 to 68)		.002
Minutes per day <50 mg/dL	13 (5 to 29)	18 (4 to 39)	6 (2 to 12)	20 (4 to 42)		.001
Hyperglycemia, median (IQR)						
Minutes per day >180 mg/dL	687 (554 to 810)	725 (537 to 798)	638 (503 to 807)	740 (625 to 854)		.03
Minutes per day >250 mg/dL	301 (190 to 401)	269 (184 to 383)	223 (128 to 351)	347 (241 to 429)		<.001
Minutes per day >300 mg/dL	129 (66 to 201)	109 (71 to 204)	78 (36 to 142)	167 (89 to 226)		<.001
Prespecified exploratory outcome						
Mean glucose, mean (SD), mg/dL	187 (27)	186 (30)	180 (27)	189 (25)	−9 (−19 to 0)	.01
Post hoc outcomes, median (IQR)[c]						
Area above curve 70 mg/dL	0.5 (0.3 to 1.1)	0.7 (0.2 to 1.4)	0.3 (0.2 to 0.5)	0.7 (0.2 to 1.3)		<.001
Area under curve 180 mg/dL	34 (25 to 46)	33 (26 to 45)	27 (17 to 40)	40 (31 to 51)		<.001

Abbreviations: CGM, continuous glucose monitoring; IQR, interquartile range.

SI Conversion: to convert glucose to mmol/L, multiply the values × 0.0555.

[a] Excludes 2 participants in the CGM group with less than 72 hours of data (a prespecified condition).

[b] Treatment group comparisons made with analysis of covariance models, adjusted for the corresponding baseline value, baseline hemoglobin A_{1c} level, and clinical site as a random effect, using pooled data from 12 and 24 weeks. Because of skewed distributions for the hypoglycemia and hyperglycemia metrics (including area above the curve 70 mg/dL and area below the curve 180 mg/dL), these models were based on ranks using van der Waerden scores. $P < .01$ was considered significant to account for multiple comparisons (with 99% CI accordingly provided for the metrics that are approximately normally distributed).

[c] Area above (the glucose) curve 70 mg/dL reflects both percentage and severity of glucose values in the hypoglycemic range. Area under (the glucose) curve 180 mg/dL is the analogous measure for hyperglycemia.

GOLD Key Results

Read the JAMA publication here.

Table 3. Primary and Secondary End Points

	CGM, Mean (95% CI)	Conventional Therapy, Mean (95% CI)	Least Square Means or Mean for Difference: CGM−Conventional Treatment (95% CI)[a]	*P* Value
Primary end point				
HbA_{1c}, %[b]	7.92 (7.79 to 8.05)	8.35 (8.19 to 8.51)	−0.43 (−0.57 to −0.29)	<.001
HbA_{1c}, mmol/mol	63 (61.6 to 64.5)	68 (66.0 to 69.4)	−4.7 (−6.27 to −3.13)	
No. of patients	142	142		
Secondary end points (sequential testing performed)[c]				
Mean glucose level, mg/dL[d]	186.93 (181.66 to 192.20)	193.68 (188.31 to 199.04)	−6.61 (−12.01 to −1.20)	.02
No. of patients	133	133		
Mean amplitude glycemic excursions, mg/dL[d]	161.93 (156.94 to 166.91)	180.96 (175.72 to 186.20)	−19.36 (−24.26 to −14.46)	<.001
No. of patients	123	127		
SD of glucose levels, mg/dL[d]	68.49 (66.36 to 70.63)	77.23 (74.96 to 79.50)	−8.69 (−10.76 to −6.61)	<.001
No. of patients	133	133		
DTSQ status version, scale total	30.21 (29.47 to 30.96)	26.62 (25.61 to 27.64)	3.43 (2.31 to 4.54)	<.001
No. of patients	136	137	131	
DTSQ change version, scale total[e]	13.20 (12.13 to 14.28)	5.97 (3.64 to 8.30)	3.76 (1.70 to 5.82)	<.001
No. of patients	69	67	136	
WHO-5 Well-Being Index	66.13 (62.94 to 69.32)	62.74 (60.18 to 65.31)	3.54 (0.61 to 6.48)	.02
No. of patients	139	140		
Hypoglycemic Fear Scale Behavior/Avoidance	1.93 (1.83 to 2.03)	1.91 (1.81 to 2.00)	0.03 (−0.05 to 0.10)	.45
No. of patients	140	140		
HCQ, scale total[f]	3.40 (3.32 to 3.47)	3.27 (3.18 to 3.35)	0.12 (0.05 to 0.19)	<.001
No. of patients	137	137	135	
Follow-up time, d	182 (180 to 187)	182 (175 to 187)		
No. of patients	142	142		

Abbreviations: CGM, continuous glucose monitoring; DTSQ, the Diabetes Treatment Satisfaction Questionnaire; HCQ, Hypoglycemic Confidence Questionnaire; WHO-5, World Health Organization-5.

[a] Least-square means (95% CIs) and *P* value were calculated using SAS procedure PROC GLM with sequence, patient (sequence), treatment period, and treatment as class variables (calculated only for normally distributed variables). For other variables in which nonparametric tests were performed, values are reported as mean (95% CI).

[b] Values are reported as last observation carried forward with HbA_{1c} measurement standardized by the National Glycohemoglobin Standardization Program.

[c] Other prespecified secondary end points and descriptive data (eTable 3 in Supplement 2) were not tested due to the rule of sequential testing (hypoglycemic fear scale-worry, problem areas in diabetes scale, percent of time with high and euglycemic levels, number and percent of patients reducing their HbA_{1c} by 0.5% and by 1%).

[d] Data were measured by CGM during 2 weeks.

[e] Data for the DTSQ change version is collected only at the end of period 2. For the CGM therapy column, it is showing the change in satisfaction from conventional therapy to CGM therapy, and for conventional therapy column, it is showing the change from CGM therapy to conventional therapy.

[f] End point defined as exploratory in the trial protocol.

--by Adam Brown and Kelly Close